Study finds leptin restores fertility, may improve bone health in lean women

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Women with extremely low body fat, including runners and dancers, as well as women with eating disorders, are prone to develop hypothalamic amenorrhea, a condition in which their menstrual periods cease, triggering such serious problems as infertility and osteoporosis.

Now, a study led by researchers at Beth Israel Deaconess Medical Center (BIDMC) offers the first definitive proof that a lack of leptin contributes to hypothalamic amenorrhea (HA) and that treatment with a synthetic form of the hormone can restore fertility and reduce the risk of bone fractures in this group of patients. The findings are reported on-line this week in the Proceedings of the National Academy of Sciences (*PNAS*).

"This condition accounts for over 30 percent of all cases of amenorrhea in women of reproductive age, and is an important problem for which we didn't have a good solution," explains senior author Christos Mantzoros, MD, Dsc, Director of the Human Nutrition Unit at BIDMC and Professor of Medicine at Harvard Medical School.

"Our findings now prove beyond any doubt that leptin is the missing link in women with significantly diminished body fat, and that this, in turn, results in numerous hormonal abnormalities." Without leptin, he explains, menstrual periods cease, the body becomes chronically energy-deprived and women experience bone loss and an increased risk of bone fractures.

Circulating leptin levels reflect the amount of energy stored in fat cells, as well as acute changes in energy intake. Shortly after leptin was discovered in 1994, the hormone generated widespread attention as a possible way to suppress the appetites of obese individuals. But studies soon found that overweight individuals had plenty of leptin and that adding more was of no benefit.

Mantzoros and his team have been examining the hormone's role from the opposite end of the energy spectrum by studying individuals with extremely low levels of body fat.

"We had known that organisms respond to famine [lack of food availability] by directing their energy into survival and away from reproduction," he explains. "And, in our initial animal studies, in the lab of Jeffrey Flier, we demonstrated that diminishing leptin levels caused by starvation had a critical role in regulating hormonal responses to food deprivation."

Over the years, work in the Mantzoros laboratory continued to bear out these initial observations. After first determining what leptin doses would be of greatest benefit, the scientists subsequently studied the hormone in groups of healthy men and women. From there, they went on to investigate women with anorexia nervosa as well as strenuously exercising women athletes, two groups known to experience multiple neuroendocrine problems including amenorrhea and brittle bones that can lead to stress fractures.

This new research – a double-blinded, placebo-controlled trial, the gold standard in scientific investigation – expands and extends pilot data from their 2004 proof-of-concept paper in the New England Journal of Medicine (NEJM), which showed that women with HA have chronically low energy and serum leptin levels.

"In this new PNAS study, we investigated 20 women between the ages of 18 and 35 who had developed HA," explains Mantzoros. "These are young, mostly college-age women, mainly runners. They watch their diets, they are slim and appear healthy. But they have abnormal hormone levels, they have ceased menstruating and stopped ovulating and they also have low bone density measures."

Over a period of 36 weeks, the study subjects were given either a synthetic form of leptin (known as metreleptin) or a placebo. (The study was conducted in a blinded randomized fashion, so that whether subjects received metreleptin or a placebo was randomly determined by a computerized algorithm, and it remained unknown to both the subjects and the treating doctors which subjects were receiving which treatment.)

The results showed that daily subcutaneous injections of replacement leptin resulted in significantly elevated levels of the hormone within just a month of treatment. "Seven of 10 women began to menstruate and four of the seven were found to be ovulating," notes Mantzoros. "Compared with the women who received the placebo, the women who received the metreleptin therapy were also found to have an improved hormonal profile and exhibited higher levels of biomarkers indicating new bone formation."

"This is a terrific example of how translational research can successfully move a discovery from the laboratory towards a therapy with tangible benefits to patients," notes Jeffrey S. Flier, MD, Dean of Harvard Medical School and a leader in the field of metabolic research whose laboratory led some of the earliest leptin investigations. "These findings suggest a role for leptin in improving a condition that results from faulty hormone signaling when levels of body fat are extremely low, and holds promise for future clinical applications."

"Helping to resolve infertility problems in these groups of women is a

critically important step," says Mantzoros. "Going forward, we will continue to examine whether metreleptin impacts not only bone markers, but also bone density and bone mineral content, key factors in helping to prevent dangerous stress fractures and osteoporosis."

Provided by Beth Israel Deaconess Medical Center